REMARKS/ARGUMENTS

Claims 1-57 are currently a part of this application. Claims 21, 22, 25, 26 and 30-57 have been withdrawn from consideration. Claims 1-20, 23, 24, and 27-29 have previously been elected for prosecution in Response to Restriction Requirement filed by the Applicant on December 12, 2006.

I. Oath/Declaration/Priority

In the Office Action, the Examiner has required that a new Oath or Declaration be filed because the originally filed Declaration is defective. A new Declaration accompanies this Response. The inventors have now properly claimed priority under 25 U.S.C. § 120.

II. Claim Objections

The Examiner has objected to Claims 2 and 3 because they recite non-elected species. Claims 2 and 3 are amended herein to address the objections. Reconsideration and withdrawal of the objection is respectfully requested.

III. Claim Rejections Under 35 USC § 112, first paragraph

The Examiner states that Claims 1-20, 23, 24, and 27-29 are rejected under 35 U.S.C. § 112, first paragraph because the specification, while being enabling for a method of detecting Alzheimer's (or other types of dementia indicated in the prior art as being enabled) comprising measuring the VGF peptide having the sequence set forth in SEQ ID NO: 11 (VGFARP-13) in the cerebrospinal fluid of patents, wherein lower levels of said VGF peptide relative to controls is indicative of Alzheimer's, wherein said method is carried out in combination with other

diagnostic methods for Alzheimer's, does not reasonably provide enablement for the claims as broadly recited.

A lack of enablement rejection under section 112, ¶ 1 is appropriate where the written description fails to teach those in the art to make and use the invention as broadly as it is claimed without undue experimentation. . . . *In re Cortright*, 49 USPQ 2d 1464, 1466 (Fed. Cir. 1999). When rejecting a claim under the enablement requirement of § 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by the claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement. *In re Wright*, 27 USPQ 2d 1510, 1513 (Fed. Cir. 1993). The question is whether the disclosure is sufficient to enable those skilled in the art to practice the claimed invention, hence the specification need not disclose what is well known in the art. *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 221 USPQ 481, 489 (Fed. Cir. 1984). According to *Fiers v. Revel*, 25 USPQ 2d 1601, 1607 (Fed. Cir. 1993), "[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken in as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." (citing, *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (C.C.P.A. 1971)).

In order to advance the present application, independent claim 1 has been amended to focus specifically on a method for detecting Alzheimer's disease or a predisposition to

Alzheimer's disease in a patient in need thereof. Applicants reserve the right to prosecute additional embodiments in continuation applications. The present specification more than adequately discloses the relationship between the VGFARP peptides and Alzheimer's disease. (Paras. [0035], [0037]-[0040]). Further, the present specification provides adequate teaching and examples to support the claim elements with regard to obtaining a biological sample from a patient (Example 1), determining the concentration of the peptides in the sample (Examples 2-4), and comparing the concentration of peptide with a control sample to elucidate the difference which indicates Alzheimer's disease or a predisposition thereto. (Example 5). The experimental processes and steps utilized in accordance with the method of claim 1, as amended, are known to those of ordinary skill in the art. Furthermore, the experimentation as set forth in the specification cannot be characterized as "undue".

In view of the amendment to claim 1 and the above arguments, Applicants submit that claim 1 is enabled under 35 U.S.C. 112, paragraph 1. Since claims 2-20 depend directly or indirectly from claim and in incorporate all the limitations of claim 1, these dependent claims are likewise enabled. Reconsideration and withdrawal of the rejection under 35 U.S.C. 112, para. 1 is respectfully requested.

Likewise, independent claim 23 has been amended to recite a method for diagnosing Alzheimer's disease in a patient and recites the same limitations as in amended independent claim 1. As such, for the same reasons as discussed above with regard to independent claim 1, claim 23 is enabled as well. Claims 24, 27 and 28 are dependent on claim 23 and are enabled since they incorporate the limitations of claim 23. Claim 29 has been canceled.

IV. Claim Rejections Under 35 U.S.C. § 102

A. Claims 1-5, 7-10, 13-16, 20, 23-24, 27-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Alberini et al. (WO 01/74298, published 11 October 2001), which is identical to the pre-grant publication, 20030166555, filed 20 September 2002.

The Examiner asserts that the claims of the instant application do not contribute anything over the prior art.

Anticipation requires the presence, in a single prior art reference, of each and every element of the claimed invention, arranged as in the claim. (*Richardson v. Suzuki Motor Co.*, 8 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989)).

Applicant traverses the rejection under 35 U.S.C. § 102 and requests reconsideration. With all due respect to the Examiner, Alberini does not anticipate claim 1 since Alberini does not recite each and every element of claim 1 arranged as in the claim. (*Richardson v. Suzuki Motor Co.*, 8 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989). (emphasis added). As amended, claim 1 of the instant invention is directed to a method for detecting Alzheimer's disease or a predisposition to Alzheimer's disease in a patient in need thereof, comprising the steps of: (1) obtaining a biological sample from said patient, (2) determining a concentration of at least one VGF protein or VGFARP peptide in the biological sample, and (3) comparing the concentration of the at least one VGF protein or VGFARP peptide in the biological sample to the concentration of the same protein or peptide in a control sample, wherein a difference between the concentration of the VGF protein or VGFARP peptide in the biological sample compared to the concentration of the VGF protein or VGFARP peptide in the control sample is indicative of Alzheimer's disease or a predisposition Alzheimer's disease.

Alberini is focused on genes that are up- or down-regulated in long term memory loss. Alberini postulates that long term memory consolidation can be modulated by treating an animal with an agent that includes, amongst others, VGF. Alberini further discloses methods for identifying agents that modulate memory consolidation and which include the steps of providing a reaction system for detecting the activity of a product, or for detecting the level of expression of a gene, the gene selected from a group that includes VGF. According to Alberini the reaction system is then contacted with a test compound and a determination is made if the test compound alters the level of expression of the gene. According to Alberini, the "reaction system" is a cell-free system (e.g., a purified protein preparation or a cell-lysate) or a whole cell system (e.g., cell-based binding assays).

Alberini does not recite the step of determining a concentration of at least one VGF protein or VGFARP peptide in the biological sample, nor the step of comparing the concentration of the at least one VGF protein or VGFARP peptide in the biological sample to the concentration of the same protein or peptide in a control sample, wherein a difference between the concentration of the VGF protein or VGFARP peptide in the biological sample compared to the concentration of the VGF protein or VGFARP peptide in the control sample is indicative of Alzheimer's disease or a predisposition to Alzheimer's disease.

Claim 1 of the instant application is explicitly focused on obtaining a biological sample for a subject, determining the amount of VGF protein or VGFARP peptide and making a comparison with a control, which in turn provides and indication of Alzheimer's disease itself of a predisposition to Alzheimer's disease. Alberini involves the use of a test compound which contacts with the reaction system to determine if there is an alteration in activity of a gene. The test compound according to Alberini can be small organic molecules, e.g., those having a

molecular weight less than 2500 amu. Alberini teaches an assessment or "measurement" method. This is unlike the method of claim 1 which provides definite indication of Alzheimer's disease or a predisposition to Alzheimer's disease.

Since each and every element of independent claim 1, as amended, is not found within Alberini, a prima facie case of anticipation has not been made. Applicant respectfully submits that claim 1 is not anticipated. Since claims 2-10, 13-16, and 20 depend directly or indirectly from amended claim 1, these claims incorporate all the limitations of amended claim 1 and are likewise not anticipated for the same reasons as asserted with regard to amended claim 1.

Independent claim 23 recites a method of diagnosing Alzheimer's disease in a patient and incorporates the same steps as set forth in amended claim 1. Alberini does not teach each and every element of independent claim 23. As such, claim 23 is not anticipated. Claims 24, and 27-29 depend directly from claim 23 and are thus also not anticipated.

Reconsideration and withdrawal of this rejection is respectfully requested.

B. Claims 1-5, 7-10, 13-16, 20, 23-24, 27-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Lo et al., US Patent No. 6,277,974. According to the Examiner, the claims of the instant application do not teach anything over Lo.

Lo is focused on the diagnosis and treatment of conditions/disorders involving cell death. The Office Action on Page 12 recites that Lo teaches methods for diagnosis of conditions, disorders or diseases involving cell death, "including, but not limited to, neurological disorders such as stroke,..." The Examiner further states that in addition to stroke, the Lo patent contemplates other diseases associated with cell death, including Alzheimer's.

As noted above in the first rejection under 35 U.S.C. 102(b), anticipation requires the presence, in a single prior art reference, of each and every element of the claimed invention, arranged as in the claim. (*Richardson v. Suzuki Motor Co.*, 8 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989)).

Lo does not recite each and every element as set forth in amended claim 1 of the instant application. Lo is principally directed to disclosing compositions and methods for the treatment and diagnosis of conditions, disorders, or diseases involving cell death. Further, Lo is directed to protective sequences (i.e., nucleic acid molecules) comprising nucleic acid sequences which, when introduced into a cell either predisposed to undergo cell death or in the process of undergoing cell death, prevent, delay, or rescue the cell from death relative to a corresponding cell into which no exogenous nucleic acids have been introduced. Lo teaches that cell death is principally the result of one of two mechanisms – apoptosis or necrosis.

Additionally, Lo is focused on treatment of stroke, which is typically characterized as resulting from an ischemic injury. Lo further states at Col. 37, lines 11-29 states that "[c]ell death programs have been increasingly implicated in Alzheimer's disease..." No positive proof connecting cell death with Alzheimer's was provided in Lo nor by the Examiner. Alzheimer's is typically characterized by protein misfolding disease, or proteopathy, due to the accumulation of abnormally folded amyloid beta protein and tau protein in the brains of Alzheimer's disease patients. (Hashimoto M, et al., (2003) "Role of protein aggregation in mitochondrial dysfunction and neurodegeneration in Alzheimer's and Parkinson's diseases.". *Neuromolecular Med* 4 (1-2): 21-36). Amyloid beta, also written Aβ, is a short peptide that is a proteolytic byproduct of the transmembrane protein amyloid precursor protein (APP), whose function is unclear but thought to be involved in neuronal development. Kerr M, et al., (2005). ("Cytoplasmic domain of the

beta-amyloid protein precursor of Alzheimer's disease: function, regulation of proteolysis, and implications for drug development.". *J Neurosci Res* 80 (2): 151-9). The presenilins are components of proteolytic complex involved in APP processing and degradation. (Cai D, Netzer W, Zhong M, Lin Y, Du G, Frohman M, Foster D, Sisodia S, Xu H, Gorelick F, Greengard P (2006). "Presenilin-1 uses phospholipase D1 as a negative regulator of beta-amyloid formation.". *Proc Natl Acad Sci U S A* 103 (6): 1941-6). This pathology differs significantly from the claims in the present application which are not directed to the administration of protective sequences, but rather are focused on providing and indication of the presence of Alzheimer's disease or a predisposition to Alzheimer's disease. The indication provided by the method of the present claims can then be used to as a diagnostic of Alzheimer's disease to reliably detect Alzheimer's at an early stage in time.

Since each and every element of independent claim 1, as amended, is not found within Lo, a prima facie case of anticipation has not been made. Applicant respectfully submits that claim 1 is not anticipated. Since claims 2-10, 13-16, and 20 depend directly or indirectly from amended claim 1, these claims incorporate all the limitations of amended claim 1 and are likewise not anticipated for the same reasons as asserted with regard to amended claim 1.

Independent claim 23 recites a method of diagnosing Alzheimer's disease in a patient and incorporates the same steps as set forth in amended claim 1. Lo does not teach each and every element of independent claim 23. As such, claim 23 is not anticipated. Independent claim 23 recites a method of diagnosing Alzheimer's disease in a patient and incorporates the same steps as set forth in amended claim 1. Alberini does not teach each and every element of independent claim 23. As such, claim 23 is not anticipated. Since claims 24 and 27-29 depend directly from amended claim 23, these claims incorporate all the limitations of amended claim 23 and are

likewise not anticipated for the same reasons as asserted with regard to amended claim 23. Reconsideration and withdrawal of this rejection is respectfully requested.

V. Claim Rejections Under 35 U.S.C. § 103

The Examiner states that the application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. The Examiner advises of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Applicant submits that the subject matter of the various claims in the present application was commonly owned at the time the inventions were made.

A. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Alberini et al. as applied to claims 1-5, 7-10, 13-16, 20, 23-24, 27-29 and further in view of Bennet et al.

The Examiner states on Page 15 of the Office Action that it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Alberini by using a combination of diagnostic methods to diagnose Alzheimer's as taught by Bennet because it is recognized that there is no definitive antemortem diagnostic test for Alzheimer's and that a multi-pronged approach to diagnosis is good clinical practice. For this same reason, the Examiner asserts, a person of ordinary skill in the art would have been

motivated to diagnose Alzheimer's using a combination of diagnostic methods. As such, the Examiner submits that the claims do not contribute anything non-obvious over the prior art.

As set forth above in response to the rejection under 35 U.S.C. § 102, claim 1 recites a specific diagnostic method that comprises the steps of determining a concentration of at least one VGF protein or VGFARP peptide in a biological sample from a patient, nor the step of comparing the concentration of the at least one VGF protein or VGFARP peptide in the biological sample to the concentration of the same protein or peptide in a control sample, wherein a difference between the concentration of the VGF protein or VGFARP peptide in the biological sample compared to the concentration of the VGF protein or VGFARP peptide in the control sample is indicative of Alzheimer's disease or a predisposition to Alzheimer's disease.

The Abstract of Bennet recites that "[t]there is not reliable antemortem diagnostic test for Alzheimer's disease;..." Bennet is dated January 1992 and reliable diagnostic methods for Alzheimer's disease were uncommon at that time. The instant claims in the present application proffer a reliable diagnostic method for indicating the presence of Alzheimer's decease or a predisposition to Alzheimer's. With all due respect, the Examiner's assertion that Alberini in combination with Bennet render claim 6 obvious is without merit.

Claim 6 depends directly from claim 1. Since dependent claim 6 incorporates all the limitations of independent claim 1 it is likewise patentable over Alberini and Bennet for the same reasons as asserted with regard to claim 1. Claim 6 and claim 1 from which it depends provides a valuable diagnostic method that is non-obvious over the prior art.

Accordingly, Applicant respectfully requests withdrawal of this rejection under 35 U.S.C. §103(a).

B. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lo et al., US Patent No. 6,277,974, as applied to claims 1-5, 7-10, 13-16, 20, 23-24, 27-29 and further in view of Bennet et al.

The Examiner states on Pages 15-17 of the Office Action that it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Lo by using a combination of diagnostic methods to diagnose Alzheimer's as taught by Bennet because it is recognized that there is no definitive antemortem diagnostic test for Alzheimer's and that a multi-pronged approach to diagnosis is good clinical practice. For this same reason, the Examiner asserts, a person of ordinary skill in the art would have been motivated to diagnose Alzheimer's using a combination of diagnostic methods. As such, the Examiner submits that the claims do not contribute anything non-obvious over the prior art.

As set forth above in response to the rejection under 35 U.S.C. § 102, claim 1 recites a specific diagnostic method that comprises the steps of determining a concentration of at least one VGF protein or VGFARP peptide in a biological sample from a patient, nor the step of comparing the concentration of the at least one VGF protein or VGFARP peptide in the biological sample to the concentration of the same protein or peptide in a control sample, wherein a difference between the concentration of the VGF protein or VGFARP peptide in the biological sample compared to the concentration of the VGF protein or VGFARP peptide in the control sample is indicative of Alzheimer's disease or a predisposition to Alzheimer's disease.

The Abstract of Bennet recites that "[t]there is not reliable antemortem diagnostic test for Alzheimer's disease;..." Bennet is dated January 1992. The instant claims in the present application proffer a reliable diagnostic method for indicating the presence of Alzheimer's

decease or a predisposition to Alzheimer's. With all due respect, the Examiner's assertion that Alberini in combination with Bennet render claim 6 obvious is without merit.

Claim 6 depends directly from claim 1. Since dependent claim 6 incorporates all the limitations of independent claim 1 it is likewise patentable over Alberini and Bennet for the same reasons as asserted with regard to claim 1. Claim 6 and claim 1 from which it depends provides a valuable diagnostic method that is non-obvious over the prior art.

Accordingly, Applicant respectfully requests withdrawal of this rejection under 35 U.S.C. §103(a).

C. Claims 11-12, 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alberini et al. (WO 01/74298) as applied to claims 1-5, 7-10, 13-16, 20, 23-24, 27-29 and further in view of Chambers et al. (J. Pathol. 200; 192:280-288).

According to the Office Action, the claims do not contribute anything non-obvious over the prior art since it would have been obvious to a person of ordinary skill in the art to modify the teachings of Alberini with the teachings of Chambers.

Claims 11-12 and 17-19 depend from independent claim 1 and incorporate all the limitations of claim 1. Claim 1 of the instant application recites a specific diagnostic method that comprises the steps of determining a concentration of at least one VGF protein or VGFARP peptide in a biological sample from a patient, nor the step of comparing the concentration of the at least one VGF protein or VGFARP peptide in the biological sample to the concentration of the same protein or peptide in a control sample, wherein a difference between the concentration of the VGF protein or VGFARP peptide in the biological sample compared to the concentration of the VGF protein or VGFARP peptide in the control sample is indicative of Alzheimer's disease

or a predisposition to Alzheimer's disease. Neither Alberini nor Chambers, alone or in combination with each other, teach such a diagnostic method as recited in claim 1 of the instant application.

With specific attention to dependant claims 11, 12 and 17-19, the Examiner relies on Alberini, in combination with Chambers, to support the asserted rejections. As set out above, Alberini does not disclose all the elements of independent claim 1. Accordingly, since dependent claims 11, 12 and 17-19 recite additional unique elements and/or limitations, claims 11, 12 and 17-19 remain patentable over the asserted combination since the cited additional reference does not supply the elements missing from Alberini with respect to the independent claim. (See, *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve,* Inc., 796 F.2d 443, 448 (Fed. Cir. 1986) ("It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art."))

Accordingly, Applicants respectfully request withdrawal of the 35 U.S.C. § 103(a) rejection of claims 11, 12 and 17-19 as being allegedly unpatentable over Alberini in view of Chambers.

D. Claims 11-12, 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lo et al., US Patent No. 6,277,974 as applied to claims 1-5, 7-10, 13-16, 20, 23-24, 27-29 and further in view of Chambers et al.

According to the Office Action, the claims do not contribute anything non-obvious over the prior art since it would have been obvious to a person of ordinary skill in the art to modify the teachings of Lo with the teachings of Chambers.

Claims 11-12 and 17-19 depend from independent claim 1 and incorporate all the limitations of claim 1. Claim 1 of the instant application recites a specific diagnostic method that comprises the steps of determining a concentration of at least one VGF protein or VGFARP peptide in a biological sample from a patient, nor the step of comparing the concentration of the at least one VGF protein or VGFARP peptide in the biological sample to the concentration of the same protein or peptide in a control sample, wherein a difference between the concentration of the VGF protein or VGFARP peptide in the biological sample compared to the concentration of the VGF protein or VGFARP peptide in the control sample is indicative of Alzheimer's disease or a predisposition to Alzheimer's disease. Neither Lo nor Chambers, alone or in combination with each other, teach such a diagnostic method as recited in claim 1 of the instant application.

With specific attention to dependant claims 11, 12 and 17-19, the Examiner relies on Lo, in combination with Lo, to support the asserted rejections. As set out above, Lo does not disclose all the elements of independent claim 1. (See, *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve,* Inc., 796 F.2d 443, 448 (Fed. Cir. 1986) ("It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art."))

Accordingly, since dependent claims 11, 12 and 17-19 recite additional unique elements and/or limitations, claims 11, 12 and 17-19 remain patentable over the asserted combination

since the cited additional reference does not supply the elements missing from Lo with respect to the independent claim.

VI. Conclusion

No fee is believed to be due for the submission of the above-listed items. If any fee should be due, the Commissioner is hereby authorized to charge any additional fee, or credit any overpayment to Deposit Account No. 03-1250, Reference No. 12080025.000035, Customer No. 43,309.

Respectfully submitted,

Date: 8/1/07

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